PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	20.07.2004
Applicant's or agent's file reference: ABL-012-PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 03/00192	07.11.2003	08.11.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/28

Applicant
ABLYNX N.V. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 08.03.2005

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-73 as originally filed

Claims, Numbers

1-49 as originally filed

Drawings, Sheets

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1-316, filed with the letter of 09.03.2004,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 22-24

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1
Inventive step (IS)	Claims	2-21,25-49
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 22-24 relate to a product defined by reference to a desirable characteristic or property, namely "an unknown agent that modulates the binding of an anti-TNF-alpha polypeptide of any of claims 1 to 11, and 13 to 16 to Tumor Necrosis Factor-alpha" (claim 22) and "an unknown agent that modulates Tumor Necrosis Factor-alpha-mediated disorders" (claim 23). The scope of claims 22-24 is unclear and speculative within the meaning of Article 6 PCT. Said claims lack indication concerning their technical features. The available experimental data actually relate to anti-TNF-alpha single domain antibodies and their preparation, but not to an agent that modulates their binding. Consequently no search has been carried out for the claims 22-24 and opinion with regard to novelty, inventive step and industrial applicability will not be established.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

NOVELTY

Reference is made to the following documents:

D1: WO 91/02078 A (PEPTIDE TECHNOLOGY LTD) 21 February 1991 (1991-02-21)

D2: VALLE E ET AL: 'Infliximab' EXPERT OPINION ON PHARMACOTHERAPY, ASHLEY, LONDON,, GB, vol. 2, June 2001, pages 1015-1025, XP002965315 ISSN: 1465-6566

D3: WO 02/057445 A (MURUGANANDAM ARUMUGAM ;STANIMIROVIC DANICA (CA); NARANG SARAM (CA)) 25 July 2002

D4: ELS CONRATH K ET AL: 'Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 276, no. 10, 9 March 2001, pages 7346-7350, XP002248402 ISSN: 0021-9258

D5: WO 02/079781 A (ANDREWS JANET S ;HESKA CORP (US); JENSEN WAYNE A (US); MCDONALD TH) 10 October 2002 (2002-10-10)

D6: TANHA J ET AL: 'Selection by phage display of llama conventional VH fragments with heavy chain antibody VHH properties' JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER, AMSTERDAM, NL, vol. 263, no. 1-2, 1 May 2002 (2002-05-01), pages 97-109, XP004354388 ISSN: 0022-1759

D7: D'HAENS G ET AL: 'ENDOSCOPIC AND HISTOLOGICAL HEALING WITH INFLIXIMAB ANTI-TUMOR NECROSIS FACTOR ANTIBODIES IN CROHN'S DISEASE: A EUROPEAN MULTICENTER TRIAL' GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 116, no. 5, May 1999 (1999-05), pages 1029-1034, XP009009036 ISSN: 0016-5085

D1 discloses monoclonal antibodies anti-TNF-alpha. The possibility that these antibodies are single domain antibodies is mentioned (p.3, l.28 - p.4, l.24 ; p.15, l.25 - l.33). The subject-matter of claim 1 dealing with an anti-TNF-alpha polypeptide comprising at least one anti-TNF-alpha single domain antibody is therefore not novel over D1.

INVENTIVE STEP

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2-17 and 21-49 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 2, and discloses (cf the references above) monoclonal antibodies against TNF-alpha and how single domain antibodies can be obtained from these antibodies. The subject-matter of claim 2 relates to a single domain antibody having a specific sequence represented by any of SEQ ID NOs: 1 to 16 and 79 to 84. It differs from D1 by the specific structures given by the sequences. These structures are associated with various effects (see the description, p.51, l.4 to p.52, l.18) among them different solubility (VHH#3E, #3G and #7B having advantageous characteristics), and different antagonistic effect (#3E and #3G being more potent antagonists then#1A (moderate antagonistic effect) or then #7B (no antagonistic effect)). Some of these effects are summarised on figure 2.

The problem to be solved by the present invention may therefore be regarded as the

provision of alternative anti-TNF-alpha single domain antibodies. The solution proposed in claim 2 appears to solve the problem posed. However since only six clones, VHH#1A, #2B, #3E, #3G, #7B and #12B (ie those corresponding to the sequences SEQ ID NOs: 1-5 and 14) were characterized, no effect was shown to be associated with the 16 clones that were not characterized. As there is no demonstrated technical effect linked to the 16 not characterized clones, these 16 clones cannot be considered to solve the problem posed, then leading to the conclusion that the subject-matter of claim 2 cannot be considered to be inventive.

While considering the part of claim 2 that is considered to solve the problem posed, ie the part dealing with the six characterized clones VHH#1A, #2B, #3E, #3G, #7B and #12B, it is considered that it does not involve an inventive step for the following reasons. Preparing single domain antibodies in llamas or camels is a known alternative to other forms of single domain antibodies that provides different advantages as disclosed in document D2 (see the abstract : soluble and functional bispecific and bivalent antibodies with the expression levels, ease of purification, the solubility and the binding capacity of the recombinant proteins being comparable with those of the constituent monomers). Therefore it is considered that a skilled person, when trying to solve the problem posed, would have used the technique of generating camelidae single domain antibodies which would have resulted in the antibodies as claimed without using inventive skills. Characterising the single domain antibodies with the sequences render the single domain antibodies novel but not inventive over the prior art.

If the applicant provides data showing particular and unexpected effects associated with some specific clones of the examples the objection concerning the inventive step could be reconsidered. However the solubility and the antagonising properties are not unexpected effects which could warrent recognition of an inventive step.

The dependent claims 3-11 and claims 12-21 and 25-49, referring to any of claims 1 to 11 do not appear to contain any additional features which, in combination with the features of claim 1, involve an inventive step as the relevant subject matter is either disclosed in the cited prior art of falls within the knowledge and ability of the skilled person. Documents D3, discloses the therapeutical use of an anti-TNF-alpha antibody, for treating rheumatoid arthtis and Crohn's disease, anticipating the subject-matter of claims 25-39 and 49.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 25-39 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLARITY

Claims 18-20 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims 18-20 attempt to define the subject-matter ("a method for identifying an agent") in terms of result to be achieved ("under conditions permitting binding between said polypeptide and target") without indicating what are the technical features of the method.